

A pharmacist led, patient tailored intervention to improve immunosuppressant medication adherence in nonadherent kidney transplant patients

Version 10 – 31/10/2017

MAIN SPONSOR: Imperial College Healthcare NHS Trust

FUNDERS: Imperial Health Charity Fund 7089

STUDY COORDINATION CENTRE: Imperial College Healthcare NHS Trust

NRES reference: 18/LO/0032

Protocol authorised by:

Name & Role	Date	Signature
Prof David Taube, Consultant Nephrologist	23/6/17	
Mr Frank Dor, Consultant Transplant Surgeon and Head of Speciality, Transplantation	23/6/17	
ICRTC Transplant Research and Audit Group	23/6/17	

Study Management Group

Chief Investigator: Dawn Goodall

Co-investigators: Prof David Taube
Dr Adam McLean
Dr Michelle Willicombe

Study Management:

1. Project steering group (to include two patients)
2. Imperial College Healthcare NHS Trust Transplant Research Group

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator: Dawn Goodall
Address: Renal and Transplant clinic
Hammersmith Hospital, W12 0HS
Tel: 0203 313 4247
Mobile: 07962258199
E-mail: dawn.goodall1@nhs.net

Clinical Queries

Clinical queries should be directed to Dawn Goodall who will direct the query to the appropriate person

Sponsor

Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London & Imperial College Healthcare NHS Trust
2nd Floor Medical School Building
St Mary's Hospital
Praed Street
London
W2 1NY
Tel: 020759 41862

Funder

Imperial College Healthcare NHS Trust

This protocol describes the pharmacist led, patient tailored intervention to improve immunosuppressant medication adherence in nonadherent kidney transplant patients study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

1. INTRODUCTION	6
1.1 BACKGROUND	6
2. STUDY OBJECTIVES	7
3. STUDY DESIGN	7
3.1 STUDY OUTCOME MEASURES	8
4. PARTICIPANT ENTRY	9
4.1 PRE-REGISTRATION EVALUATIONS	9
4.2 INCLUSION CRITERIA	9
4.3 EXCLUSION CRITERIA	9
4.4 WITHDRAWAL CRITERIA	10
5. ADVERSE EVENTS	10
5.1 DEFINITIONS	10
5.3 REPORTING PROCEDURES	10
6. ASSESSMENT AND FOLLOW-UP	11
7. STATISTICS AND DATA ANALYSIS	11
8. REGULATORY ISSUES	12
8.1 ETHICS APPROVAL	12
8.2 CONSENT	12
8.3 CONFIDENTIALITY	12
8.4 INDEMNITY	12
8.5 SPONSOR	12
8.6 FUNDING	13
8.7 AUDITS AND INSPECTIONS	13
9. STUDY MANAGEMENT	13
11. PUBLICATION POLICY	13
12. REFERENCES	ERROR! BOOKMARK NOT DEFINED.
EXAMPLE APPENDICES	13
APPENDIX 1. SUMMARY OF INVESTIGATIONS, TREATMENT AND ASSESSMENTS	13

GLOSSARY OF ABBREVIATIONS

ACR	Acute cellular rejection
AMR	Antibody mediated rejection
CNI	Calcineurin inhibitor
DNA	Did not attend
DSA	Donor specific antibody
eGFR	Estimated Glomerular filtration rate
IPV	Inpatient variability

KEYWORDS

Medication adherence
Nonadherence
Clinic attendance
Inpatient variability
Tacrolimus
Kidney transplant

STUDY SUMMARY

TITLE A pharmacist led, patient tailored intervention to improve immunosuppressant medication adherence in nonadherent kidney transplant patients

DESIGN Prospective, multidimensional cohort study

AIMS The aim of the study is to determine prospectively, whether patients who receive regular, intensive, pharmacist led, tailored medication adherence support will demonstrate an improved adherence to their medication regime resulting in a reduction in the observed inpatient variability (IPV) of tacrolimus trough levels and improved attendance at out-patient clinic appointments

OUTCOME MEASURES Difference in immunosuppression medication adherence before and after the intervention

Difference in the median IPV before and after the intervention

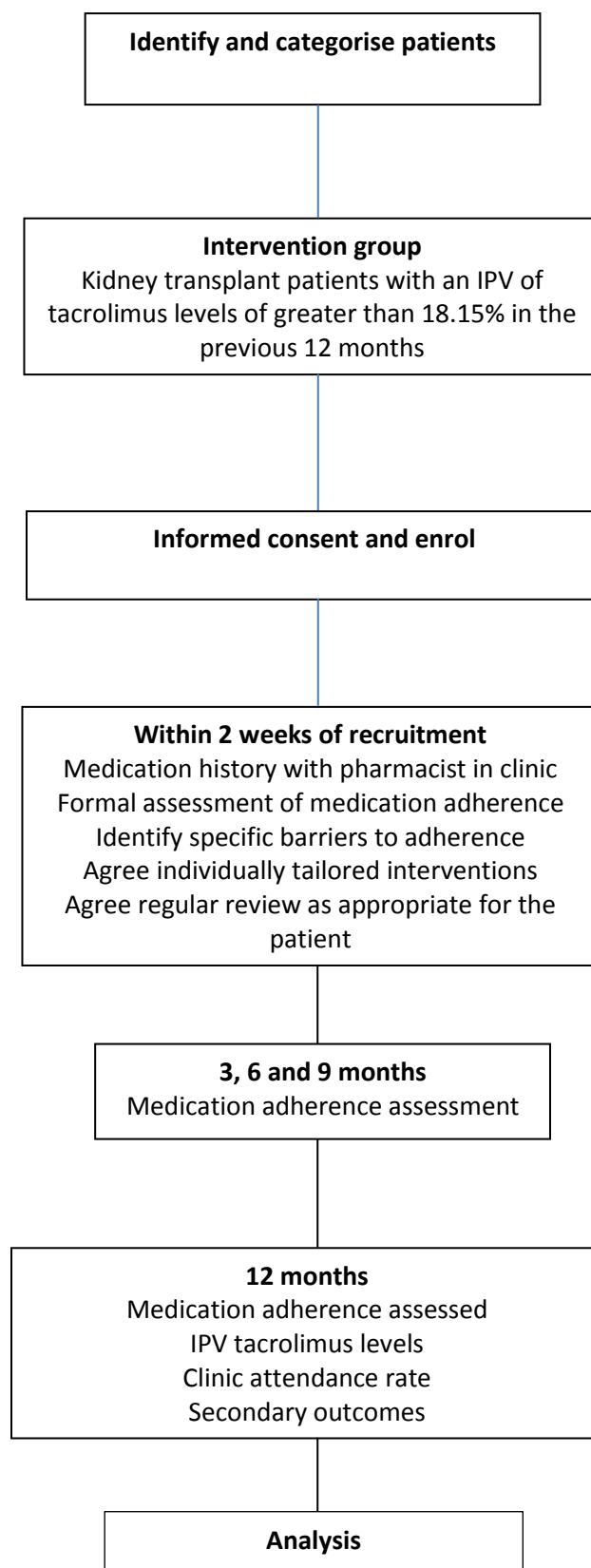
Difference in outpatient clinic nonattendance rate before and after the intervention

POPULATION Adult kidney transplant patients

ELIGIBILITY Kidney transplant patients with a high IPV of their tacrolimus levels

DURATION One year

REFERENCE DIAGRAM



1. INTRODUCTION

1.1 BACKGROUND

Organs for transplantation remain a scarce and precious resource with over 5000 patients currently on the kidney transplant waiting list. A kidney transplant costs approximately £17,000 in the first year and £5,000 per subsequent year. If the transplant fails, the patient must return to dialysis at an estimated cost of £30,800 per year or be retransplanted. While short term outcomes have improved steadily over the last 15-20 years, longer term outcomes haven't and after 10 years approximately 30% of kidney transplants have failed.

Nonadherence to immunosuppressive medication is increasingly being associated with these poor long term outcomes (1-10) as it has been shown to be a potent risk factor for the development of de novo donor specific antibody (DSA) and antibody mediated rejection (AMR) with AMR being a leading cause of kidney transplant failure(11-14). In a prospective study undertaken by Sellares et al(11) investigating the causes of kidney transplant failure in a series of patients who underwent an indicative biopsy it was shown that 64% of the transplants that failed were due to rejection, every rejection loss had evidence of AMR by the time of failure and among the rejection losses, 47% were independently identified by their clinician as being nonadherent. A study by Pinsky et al reported that not taking immunosuppressive medications as prescribed (defined as taking medication <95.1% of days) is associated with a 60% increased risk of kidney transplant failure(15).

Studies have estimated that 30-50% of transplant patients are nonadherent to their immunosuppressive medication(1, 4, 6, 16) and that graft loss is seven times more likely in a nonadherent compared to an adherent patient(17). Nonadherence to immunosuppression can start at any time after the transplant; sometimes within weeks but also after months or years(4, 18). A prospective cohort study undertaken by Massey(18, 19). and colleagues identified that self-reported nonadherence to immunosuppression medication increased significantly between 6 weeks and 6 months post-transplant from 17% to 27% and that by 18 months, the rate of nonadherence had reached 31%. They assessed patient's perceptions of the importance of medication adherence over time and while it was initially high, it decreased significantly over time.

In a meta-analysis of adherence rates among solid organ transplant recipients, nonadherence to immunosuppression medication was shown to be the highest in the kidney transplant recipients at 35.6 cases per 100 persons per year (PPY) compared to 14.5 cases per 100 PPY for heart recipients and 6.7 cases per 100PPY for liver recipients(20). This higher rate of nonadherence in the kidney transplant recipients is possibly because the consequences of nonadherence are higher in other SOTs. Adherence with therapy is one of the criteria when listing a patient for transplant and it is possible that recipients of SOTs other than the kidney may be subject to more stringent psychosocial selection criteria.

There are many reasons why patients do not adhere to their medication and their barriers to adherence can change over time. Patients who are nonadherent to immunosuppressant medication will often be nonadherent to other medicines prescribed for them, clinic attendance, diet, exercise, alcohol consumption, smoking and illicit drug use(1, 16). All of these factors will contribute to the overall morbidity and mortality of the patient.

1.2 RATIONALE FOR CURRENT STUDY

Nonadherence to immunosuppressive medication post kidney transplant is a potent risk factor for rejection and graft loss. Clinicians often have little time to discuss medication adherence in detail with patients in the outpatient clinic and while pharmacists would be well placed to take on this role, they are under-utilised and under-resourced in transplant outpatient clinics. The aim of this study

will be to determine prospectively, using a multidimensional design, whether immunosuppression medication adherence can be improved in a group of patients receiving tailored medication adherence support from a pharmacist resulting in a reduction in the observed inpatient variability (IPV) of tacrolimus trough levels and an improved attendance at outpatient clinic appointments. Adherence support will be provided for one year and will be individualised to each patient in the intervention group after identifying both their practical and perceptual barriers to adherence. A range of clinical outcomes will be assessed for all patients on a regular basis in order to determine whether the provision of effective medication adherence support for our kidney transplant patients may help to optimise the long-term outcomes of these transplants.

2. STUDY OBJECTIVES

To improve immunosuppression medication adherence with pharmacist led, patient tailored adherence support

To improve IPV of tacrolimus levels with pharmacist led, patient tailored adherence support

To improve attendance at outpatient clinic appointments with pharmacist led, patient tailored adherence support

To determine if there is a correlation between IPV of immunosuppression levels and the self-reported and objectively measured adherence of the patient

3. STUDY DESIGN

A prospective, multidimensional cohort study to include 42 kidney transplant patients with a high IPV of their tacrolimus levels from Imperial College Renal and Transplant Centre Outpatient Clinic. Patients recruited into the study will receive pharmacist led, patient tailored interventions to improve immunosuppressant medication adherence. Patients will be included in the study for one year from recruitment.

Intervention:

Patients will receive regular, intensive, personalised support from a pharmacist to improve adherence to immunosuppressive medications. The pharmacist will meet with the patient on a regular basis in the transplant outpatient clinic to identify their perceptual and practical barriers to adherence and agree a support plan that is tailored to them.

Within the first two weeks of recruitment, the study pharmacist will meet with the patient in the transplant outpatient clinic to:

- Undertake a full medication history
- Discuss self-reported medication nonadherence
- Undertake the BAASIS questionnaire
- Ask the patient to complete a Beliefs about Medicines Questionnaire (BMQ)
- Undertake a socioeconomic and educational assessment
- Undertake to gain collateral reporting of nonadherence by clinicians, relatives, friends or carers
- Perform a tacrolimus pill count
- Check in-house dispensing records of tacrolimus
- Identify barriers to adherence

- Tailor interventions and support to the needs of the patient
- Complete a motivational interview
- Agree to meet again during an outpatient clinic visit within an agreed time which is appropriate for the patient needs and within 3 months

This first visit will provide a baseline assessment of the patient's medication adherence.

Tailored interventions and support may include:

- Setting alarms
- Medication diary card or calendar
- Medication compliance aid filled by the patient, family/carers or by a pharmacy professional
- Adherence app
- Reducing the complexity of the medication regime
- Positioning medication within their daily routine eg. by toothbrush
- Changing formulations
- Additional education regarding need for medication / timing of doses
- Referral to a social worker to assist with affordability of medicines
- Referral to a psychologist to explore deeper psychological issues regarding medicines taking

The structure of each follow up adherence review will be the same as the first formal adherence review with the exception that the BMQ will only be repeated at the end of the one year follow-up and the socioeconomic and educational assessment will only be undertaken at the first assessment review. Every patient will have a formal adherence assessment at 3, 6, 9 and 12 months. At the end of one year of follow-up, the specific benefits perceived by the patient of intensive adherence support from a pharmacist will be determined through a questionnaire.

Baseline nonadherence will be measured at the first visit with the study pharmacist within two weeks of recruitment and then at 3, 6, 9 and 12 months. The IPV of their tacrolimus levels and their outpatient clinic nonattendance rate will be measured retrospectively in the 12 months prior to recruitment to the study and then prospectively at the end of the intervention year.

3.1 STUDY OUTCOME MEASURES

Primary outcome measures

1. Difference in adherence to immunosuppression medication measured by:
 - Self-reporting of nonadherence by the patient
 - BAASIS questionnaires
 - Collateral reporting of nonadherence by clinicians, relatives, friends or carers
 - Tacrolimus pill counts
 - In-house dispensing records of tacrolimus

Nonadherence will be scored using the Imperial College Renal and Transplant Centre classification of immunosuppressant medication nonadherence tool.

2. Difference in the median IPV before and after the intervention year
3. Difference in outpatient clinic nonattendance rate before and after the intervention year

Secondary outcome measures

Allograft outcome:

- Biopsy proven ACR/AMR
- Development of a DSA or transplant glomerulopathy
- Development of fibrosis, hyalinosis, calcineurin inhibitor (CNI) toxicity or diabetic change on biopsy
- Graft loss
- Death

Allograft function:

- Serum creatinine
- eGFR
- Proteinuria
- Haematocrit
- Albumin
- Haemoglobin
- Tacrolimus levels

Other:

- Readmissions

Standard blood tests will be performed at every clinic visit.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Adult kidney transplant patients with a functioning graft who have shown a pattern of nonadherent behaviour for at least six to twelve months prior to recruitment. Nonadherence will be demonstrated by a high IPV of their tacrolimus levels

4.2 INCLUSION CRITERIA

Adult kidney transplant patients (18 years of age and above)

Kidney transplant patients with an IPV of tacrolimus levels of greater than 18.15% in the previous 12 months

4.3 EXCLUSION CRITERIA

Antibody incompatible transplants including patients with preformed HLA and blood group incompatible

Previous rejection

Donor specific antibody positive

HIV positive patients

Simultaneous pancreas and kidney patients

Paediatric patients (less than 18 years of age)

4.4 INCLUDE IN IPV ANALYSIS

Outpatient tacrolimus levels measured retrospectively in the 12 months prior to recruitment

Outpatient tacrolimus levels measured prospectively 12 months after recruitment

Patients who develop a DSA or rejection during the study will only have their tacrolimus levels prior to the event included in the analysis

Patients who switch to Advagraf® during the study will only have their tacrolimus levels prior to the switch included in the analysis

4.5 EXCLUDE FROM IPV ANALYSIS

All inpatient tacrolimus levels

Tacrolimus levels during the period of instability caused by a significantly interacting co-prescribed medication

4.6 WITHDRAWAL CRITERIA

Death

Graft loss

Transfer out of unit

Loss of capacity

Identifiable data already collected with consent would be retained and used in the study. No further data would be collected or any other research procedures carried out on or in relation to the participant

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to kidney transplantation and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Riverside Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Fax 0208 383 8543, attention Dawn Goodall
Please send SAE forms to: Dawn Goodall
Tel: 0208 383 4247 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

All patients will be followed up in the transplant outpatient clinic at regular intervals as per current practice. Those enrolled in the study will be followed for 12 months and will have additional medication adherence assessments with the study pharmacist as outlined in section 3 (study design).

The study will end following one year of adherence intervention and assessment for all patients enrolled in the study.

7. STATISTICS AND DATA ANALYSIS

The trial is powered (Type I error (α) 0.05 type II error (β) 0.10) to show a difference in IPV before and after the intervention of 35%. This predicted difference is based on clinical experience and judgment. An overall sample size of 42 patients will be recruited. An unlikely 20% losses (33 patients recruited and retained in the study) would result in an 80% power of demonstrating the same difference (Type I error (α) 0.05 type II error (β) 0.20).

Standard and transplant specific demographics will be collected for all patients. Outcome data will be collected through interrogation of the hospital information system. Statistical analyses will be carried out using Medcalc or SPSS. Data will be summarised as mean (SD) for continuous variables and number of subjects (percent) for categorical variables. Chi-square and t-tests will be performed

to determine significant differences in immunosuppressant medication adherence, IPV and clinic attendance before and after the intervention year.

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the Riverside Research Ethics Committee and the HRA. The Chief Investigator will require a copy of the Trust Capacity and Capability approval email before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. Formal written consent will be obtained by a member of the research team at the time of recruitment in the Renal and Transplant Clinic at Hammersmith Hospital.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. The Chief Investigator and other members of the research team are members of the healthcare team caring for the participants therefore have access to their personal information. Confidential patient information will be stored only on the Trust computer systems, all of which are password protected and will not be shared with anyone outside of the research or healthcare team. Non-anonymised data will be available to study clinicians only. Electronic data will be pseudonymised prior to analysis (ie each patient = unique number) and stored on the secure hospital systems all of which are password protected. Signed consent forms will be scanned onto the patient's electronic record then destroyed. Non-anonymised data will be available only to members of the research team and will be stored only on the Trust computer systems, all of which are password protected and will not be shared with anyone outside of the research or healthcare team.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study. Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study (delete as applicable)

8.5 SPONSOR

Imperial College Healthcare NHS Trust will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

Imperial Health Charity fund 7089 are funding this study.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through a study specific steering group and the Imperial College Renal and Transplant Centre Research Group.

10. PUBLICATION POLICY

The outcomes of this study will be published in a high impact peer reviewed journal

11. SUMMARY OF INVESTIGATIONS, TREATMENT AND ASSESSMENTS

Exam		Month of Treatment – clinic appointments will vary. This is an example only											
	Pre-recruitment	1	2	3	4	5	6	7	8	9	10	11	12
Informed consent	X												
Clinic attendance	X			X			X			X			X
IPV tacrolimus levels	X			X			X			X			X
Medication adherence review		X		X			X			X			X

12. APPENDICES

Appendices should be additional information to the protocol and can consist of:

- Participant Information Sheet
- Consent form
- GP letter
- Questionnaire to measure the specific benefits perceived by the patient of intensive adherence support from a pharmacist
- Classification of immunosuppressant medication nonadherence tool
- BAASIS questionnaire

REFERENCES

1. Kidney Disease: Improving Global Outcomes Transplant Work G. KDIGO clinical practice guideline for the care of kidney transplant recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2009;9 Suppl 3:S1-155.
2. De Bleser L, Matteson M, Dobbels F, Russell C, De Geest S. Interventions to improve medication-adherence after transplantation: a systematic review. *Transplant international : official journal of the European Society for Organ Transplantation*. 2009;22(8):780-97.
3. Denhaerynck K, Steiger J, Bock A, Schafer-Keller P, Kofer S, Thannberger N, et al. Prevalence and risk factors of non-adherence with immunosuppressive medication in kidney transplant patients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2007;7(1):108-16.
4. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Evans R, et al. Nonadherence consensus conference summary report. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2009;9(1):35-41.
5. Gaston RS, Hudson SL, Ward M, Jones P, Macon R. Late renal allograft loss: noncompliance masquerading as chronic rejection. *Transplantation proceedings*. 1999;31(4A):21S-3S.
6. Morrissey PE, Flynn ML, Lin S. Medication noncompliance and its implications in transplant recipients. *Drugs*. 2007;67(10):1463-81.
7. Morrissey PE, Reinert S, Yango A, Gautam A, Monaco A, Gohh R. Factors contributing to acute rejection in renal transplantation: the role of noncompliance. *Transplantation proceedings*. 2005;37(5):2044-7.
8. Prendergast MB, Gaston RS. Optimizing medication adherence: an ongoing opportunity to improve outcomes after kidney transplantation. *Clinical journal of the American Society of Nephrology : CJASN*. 2010;5(7):1305-11.
9. Schafer-Keller P, Steiger J, Bock A, Denhaerynck K, De Geest S. Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2008;8(3):616-26.
10. Wiebe C, Nevins TE, Robiner WN, Thomas W, Matas AJ, Nickerson PW. The Synergistic Effect of Class II HLA Epitope-Mismatch and Nonadherence on Acute Rejection and Graft Survival. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2015;15(8):2197-202.
11. Sellares J, de Freitas DG, Mengel M, Reeve J, Einecke G, Sis B, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2012;12(2):388-99.
12. Roberts DM, Jiang SH, Chadban SJ. The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. *Transplantation*. 2012;94(8):775-83.
13. Wiebe C, Gibson IW, Blydt-Hansen TD, Karpinski M, Ho J, Storsley LJ, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2012;12(5):1157-67.

14. Hughes s, De Freitas, D, Worthington, J., Strickland-Hodge, B. Preventing donor-specific antibodies after transplant. *Clinical Pharmacist*. 2014(Jan / Feb 2014).
15. Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2009;9(11):2597-606.
16. Organisation WH. ADHERENCE TO LONG-TERM THERAPIES
Evidence for action. World Health Organisation; 2003. Report No.: WHO/MNC/03.01.
17. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. *Transplantation*. 2004;77(5):769-76.
18. Massey EK, Tielen M, Laging M, Timman R, Beck DK, Khemai R, et al. Discrepancies between beliefs and behavior: a prospective study into immunosuppressive medication adherence after kidney transplantation. *Transplantation*. 2015;99(2):375-80.
19. Massey EK, Tielen M, Laging M, Beck DK, Khemai R, van Gelder T, et al. The role of goal cognitions, illness perceptions and treatment beliefs in self-reported adherence after kidney transplantation: a cohort study. *Journal of psychosomatic research*. 2013;75(3):229-34.
20. Dew MA, DiMartini AF, De Vito Dabbs A, Myaskovsky L, Steel J, Unruh M, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation*. 2007;83(7):858-73.